Remarks

Claims 1, 2 and 11-17 are pending. Claims 2, 12 and 13 have been amended. Claims 2, 12 and 13 are amended to more clearly claim what applicants consider to be their invention. No new matter is added by these amendments. Also, since the amendments include only language that was already examined, and since they are what the Office has stated is acceptable, no new issues are presented. Therefore entry of the amendments is believed to be merited and is respectfully requested. In view of the above amendments and the following remarks reconsideration and further examination are respectfully requested.

Claim Rejections - 35 USC § 112

Claims 2, 12, and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action states that claims 2, 12, and 13 are indefinite in their recitation of "wherein the nucleic acid is delivered intranasally" (or via aerosol or via the airway) because it is unclear if only the nucleic acid is delivered "intranasally" (or via aerosol or via the airway) or if the entire AAV5 particle is delivered by the route recited in the claim. The Office Action suggests amending the claim to recite "wherein the AAV5 particle is delivered ..." would be remedial.

Applicants have amended claim 2, 12 and 13 to recite "wherein the AAV5 particle is delivered ..." with support as found in the claims as filed. In keeping with the statement in the Office Action, this should overcome the rejection, and its rejection is respectfully requested.

Claim Rejections - 35 USC § 103

Claim 11, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,180,613 (Kaplitt et al., filed June 6, 1995) and Georg-Fries et al. (1984). The Office states the following:

> The claims are directed to delivering a nucleic acid to a cerebellar cell by administering an AAV5 particle containing a nucleic acid inserted between a pair of AAV inverted terminal repeats. Claim 15 specifically recites that the AAV5 particle is delivered directly to the brain of a subject.
>
> Kaplitt et al. disclose a method for ameliorating a symptom of a central nervous system disorder in a mammal by administering an AAV vector to a target cell in the brain of the mammal. See Claim 1. Claim 11 specifically recites that the target cell is in the cerebellum. The specification and the claims read broadly on AAV vectors of any subtype, including AAV-5. Claim 1 specifically recites that the method comprises direct administration of an AAV vector to a target cell in the brain.
>
> Georg-Fries et al. (1984) disclose that the type 5 adeno-associated virus has been known in the art since 1984.
>
> Since AAV5 has been known in the art since 1984 and further since the claims of Kaplitt et al. read broadly on AAV vectors of any subtype, it is evident that in 1995 Kaplitt contemplated using AAV5 vectors, as well as AAV vectors of other subtypes, in practicing the claimed methods.
>
> Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.
>
> At pages 11-12 of the response, Applicants argue that Georg-Fries et al. provides no AAV5 sequences and that it is the present application that discloses how to utilize the AAV5 genome and its subsequences as vectors to deliver nucleic acids to cerebellar cells. Applicants further argue that Kaplitt, et al. provides no AAV5 sequences nor any guidance as to how to utilize the AAV5 genome and its subsequences for delivery of nucleic acids to a cerebellar cell. Applicants therefore argue that there is no reasonable expectation of success. Although Kaplitt et al. does not provide AAV5 sequences it would be routine for one of skill in the art to obtain these sequences and use them in the same manner as sequences from other AAV subtypes. Since the patent claims read broadly on any AAV vector it is evident that the Office considers the claims to be enabled for any AAV serotype. Further, since the claims of Kaplitt et al. are not limited to the specific AAV serotype exemplified in the working example, it is evident that the

> Office accepts that the claims are broadly enabled for any AAV serotype and that only routine experimentation is required to use other AAV serotypes. Since only standard molecular biology and cloning techniques are required to use the AAV5 serotype instead of another AAV serotype, one of skill in the art would have a reasonable expectation of success for using an AAV5 vector in the method disclosed by Kaplitt et al. (Emphasis added.)

The present method of using AAV5 to transduce cerebellar cells is an important advancement in this field, and is so recognized by the skilled artisan. For example, the Davidson et al. paper (PNAS, 2000, 97:3428-3432, filed with the original IDS) describes AAV5 transduction in the CNS. It has been cited 94 times since it was published. Furthermore, the Lee et al. paper makes reference to applicants' important discovery. "The AAV5-derived vectors were found to be more efficient than AAV2-derived vectors for gene transfer to muscle, liver and ependymal cells in the cerebral ventricles and hemispheres (Davidson et al., 2000; Chao et al.; 2000; and Mingozzi et al., 2002)" (page 75, right column). Applicants claimed and currently rejected invention was accepted for publication in PNAS, a very highly regarded and competitive peer review journal. This journal is known to publish cutting-edge (non-obvious) research. This fact, by itself, shows that those skilled in this art as recently as 2000 did not view the claimed use of AAV5 as obvious. Thus, the Office's position that the present claim is obvious cannot be said to be based on what one of skill in the art would have believed at the time the present application was filed. Since a sustainable finding of obviousness must be based on the perspective of one of ordinary skill in the art at the time of the invention, the present rejection fails for lack of correlation with the required standard.

The Office also fails to make out a prima facie case of obviousness. Applicants traverse on the ground that there is no combination of art that suggested using AAV5 to transduce cerebellar cells. In support of this traversal, applicants provide: 1) evidence from the art showing

that obtaining and sequencing AAV5 nucleic acids is not routine and 2) evidence from the art showing that it was not routine to use AAV5 sequences as a vector. Furthermore, applicants traverse on the ground that it is improper for the Office to infer a teaching into a patent specification based on the presumed enablement of a claim of that patent.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the references must teach or suggest all the claim limitations.

Regarding motivation to use AAV5 as a vector, Georg-Fries et al. provides no motivation, because it teaches nothing about AAV5 that would hint at any usefulness as a vector. Kaplitt et al. provides no motivation to use AAV5 either generally as a vector or specifically in the method it discloses for AAV2, because it discloses nothing about AAV5 and provides no suggestion that AAV5 would contribute anything that AAV2 did not do. Furthermore, Kaplitt et al. provides no motivation for use of any AAV to transduce any cerebellar cells, because it never tested any AAV, including the AAV2 disclosed, in any cells of the cerebellum. Due to the lack of relevant teaching in this combination of art, a skilled person would not have been motivated to try AAV5 in the method of the present invention. For the reasons stated below, the skilled person would also not have had a reasonable expectation of success.

Regarding a reasonable expectation of success, there is no scientific basis to believe that the prior art provided a reasonable expectation of success doing what applicants claim in the rejected claims. In fact, neither the cloning and sequencing of AAV5 nor the use of AAV5 or its components as a vector were routine. The general lack of knowledge of AAV5, the specific lack

of knowledge of the tropism(s) of AAV5, and the difficulties cloning and sequencing AAV5 are highlight in the art described below.

The Cloning of AAV5 by applicants was not routine nor was it expected by the skilled artisan to be routine. Harold zur Hausen is a world renowned virologist and head of the DKFZ, the premier institute in Germany for virus research. Bantel-Schaal et al. (Journal of Virology, 1999:939-947, attached as Exhibit A) writes regarding their attempt to clone AAV5, that they were only able to clone 95% of the genome and were not able to clone the ITRs (paragraph bridging pages 939 and 940). More specifically, they write: "Although up to now we were not able to determine the complete terminal sequence of AAV5, the approximate length of the genome could be deduced. On the basis of the position of the trs about 100 additional nucleotides are expected at each end of the DNA molecule" (page 942, right column). They also write: "Since we did not succeed in reading the entire sequence of the AAV5 genome, we used the terminal resolution site and the respective inverted sequence (50) (Fig. 2B) as reference positions for aligning the partial AAV5 sequence to the published DNA sequences of AAV2, AAV3B, AAV4, and AAV6" (page 943, right column). They further state that they "have determined the sequence of 4,404 nt (about 95% of the estimated size of 4.5 to 4.6kb) of the AAV5 genome, but up to now we were not able to resolve the complete sequence of the terminal repeats (page 946, left column). Thus, it cannot be said that obtaining the sequence of AAV5 could have been routine, or would have been considered routine, when a renowned expert in the field has experienced difficulty.

A recent paper by Lee et al. (Journal of Virological Methods, 111(2003):75-84, attached as Exhibit B) notes the difficult with cloning AAVs in general:

> All direct molecular cloning with the AAV genome starts with either single-stranded viral DNA or double-stranded intermediate, and this leads to a string of steps involving the annealing of complementary single strands, end-filling, attaching linkers, selecting a lower-copy number plasmid, blunt-end ligation, colony selection through hybridization, and finally reassembling subgenomic fragments (Chiorini et al., 1999; Samulski et al., 1982; Laughlin et al., 1983; Hermonat and Muzyczka, 1984; Xiao et al., 1999; Muramatsu et al., 1996; Chiorini et al., 1997; Qiu et al., 2002). Many of these step manipulations take time and infrequently generate positive results, and thus, require elaborate efforts to obtain the final infectious clone often at a probability of less than 10% (Samulski et al., 1982; Senapathy and Carter, 1984). Such attempts have experienced difficulties in terms of isolating full-length infectious AAV clones in a single step, in fact infectious viral genomes have been usually obtained by reassembling cloned subgenomic fragments (Laughlin et al., 1983; Xiao et al., 1999; Muramatsu et al., 1996; Chiorini et al., 1997; Qiu et al., 2002).
>
> Paragraph bridging pages 75 and 76

These references show that even after the time that the present inventors cloned and sequenced AAV5, the skilled person in this field did not view it as routine to obtain AAV sequences in general and AAV5 sequences specifically. This evidence of the state of the art contradicts the Office's assertion, which is without any cited scientific support, that it would be routine to obtain the AAV5 sequences necessary for its use as a vector.

Regarding any use for AAV5 prior to the present invention, the art provides no teaching that would have suggested the use of the present method claims. For example, Bantel-Schaal et al. 1984 (Virology, 1984, 134:54-62, attached as Exhibit C) teaches that AAV5 is divergent from other known AAVs. A cross hybridization of genome by Southern blot demonstrated that AAV5 shared only distant homology with AAV2, 3. More specifically, comparison of the DNAs showed that AAV5 is different from the other 4 AAV serotypes that have been found in man and monkey so far, not only in the size of its DNA but also in DNA homology. The reference teaches that "the serotypes AAV 1- AAV 4 shares more homologies with each other than they do

with AAV 5" (page 58, left column). The reported differences from other AAVs (particularly AAV2, which was the only AAV known as a vector prior to the present invention) teaches against the likelihood that AAV5 could be successfully used as a vector. In fact, AAV2 was first shown to work as a vector in October 1984 by Hermonat, P. L., and N. Muzyczka (Use of adeno-associated virus as a mammalian DNA cloning vector: transduction of neomycin resistance into mammalian tissue culture cells. Proc. Natl. Acad. Sci. USA 81:6466–6470). There is neither suggestion nor any guidance in Bantel-Schaal for any use for AAV5. Rather, this art is one of several references that contradicts the assertion by the office action that using AAV5 as a vector would have been reasonably expected by the skilled person to be successful prior to the present application.

Georg-Fries et al. 1984 (of record) also teaches that AAV5 is distinct from other AAVs. They show that 3 AAV5 proteins, that are similar but distinct in size from AAV3 specific proteins, can be immunoprecipitated from infected cell preparations. However, this work also teaches that AAV5 seroreactivity in a patient population is distinct from that of AAV1, 2, 3 and suggests a different lifecycle and nature helper virus for AAV5 compared to AAV1, 2, 3. Georg-Fries only provides enough information about AAV5 to raise a significant doubt in the mind of the skilled person about its usefulness as a vector. In any case, this reference provides no guidance as to how AAV5 might be used.

In summary, it can be seen that the only references which provided any information at all about AAV5 prior to the present invention (Georg-Fries et al. and Bantel-Schaal et al.) discussed differences with other AAVs that would have prevented the skilled person from having a reasonable expectation of success in using AAV5 as a vector. This taken in combination with

the fact that there was not even a reasonable expectation of obtaining the needed sequences, provides a picture of prior art that provides no reasonable expectation of success. The state of the art at the time Kaplitt et al. was filed showed that the lifecycle of AAV5 is distinct from that of AAVs1, 2, 3 and 4, and therefore it would not have been obvious to the skilled person that methods used to produce recombinant vectors based on AAV2 would work with AAV5. More pertinently, nothing in the AAV prior art suggested (i.e., provided a reasonable expectation) that AAV5 could be used in the same method as taught by Kaplitt et al. for AAV2. Furthermore, there is no disclosure in Kaplitt et al. that supplies the essential guidance regarding AAV5 that is missing from the other AAV art.

The current rejection is improper, because it relies on an imputed suggestion that is simply not present in any prior art. Because there is no explicit or implicit suggestion in Kaplitt et al. of using AAV5 to transduce cerebellar cells, and there is no suggestion in Georg-Fries et al. regarding any vector use of AAV5, the combination of Kaplitt et al. and Georg-Fries et al. does not suggest all of the limitations of the rejected claims.

The Office uses the presumption of validity (i.e., enablement) of an issued claim to infer back into the specification of Kaplitt et al. the teaching it relies on for its prima facie case of obviousness. The Office infers contemplation, thus written description and enablement, into the Kaplitt et al. patent only because the Office issued a generic claim that the Office asserts reads on the specific claim of the present invention. Contemplation requires some evidence that applicants actually considered what is said to be contemplated. Kaplitt et al. lacks any evidence of contemplation of the use of AAV5 as a vector.

Kaplitt et al. never contemplated using a different serotype than AAV-2. No mention is made of any isolate of AAV other than type 2. Furthermore, all the references cited in Kaplitt, et al. describe only AAV-2, not other serotypes. The methods taught are effective only for AAV2, not AAV5. For example, Figure 1 and 2 are maps of plasmids used in the experiments and are based on AAV2. Production of AAV5 based vectors would require a different set of plasmids not taught in Kaplitt et al. or any other art. In fact, the plasmids needed for making an AAV5 vector were not known at the time Kaplitt et al. was filed, and could not have been made until applicants' cloning of AAV5.

Kaplitt et al. never mention other serotypes, much less suggest that other serotypes may have different tropisms and could be used to target specific cell types. Furthermore, Kaplitt et al. discuss many details of their invention, for example, the sources and natural history of AAV2, the importance of the use of various promoters (regulated promoters, ubiquitous promoters, tissue specific promoters: column 15-16) and that for targeting of a vector to a specific cell type it may be necessary to "associate the vector with a homing agent that binds specifically to a surface receptor of the cell." However, they never mention the use of other serotypes of AAV or the use of proteins from other AAV serotypes as embodiments of their application. There is no description in Kaplitt et al. that suggests, much less establishes, any contemplation of the use of AAV5 in the methods they teach.

When read in context, it can be seen that the use of the phrase "AAV vectors" by Kaplitt et al. refers to the multiple AAV2 vectors, LacZ or hTH, used in their study and not the use of different isolates of AAV. The statement that "[t]he present invention is the first demonstration that AAV vectors can safely and efficiently transfer and express a foreign gene marker gene

(lacZ) in the adult rat brain" refers to AAV2 LacZ vector ("pAAVlac") and AAV2 hth vector (pAAVth). There is no disclosure in the Kapplit et al. specification to suggest any other interpretation.

In addition to having no teaching, whatsoever, regarding AAV5, Kaplitt et al. only teach about the use of AAV2 vector (psub201 based vectors) for transduction of neurons in the hippocampus, substantia nigra, and striatum (column 17). These neurons are physically and spatially distinct from the cerebellar cells targeted by AAV5 vectors that are claimed in the present application. While Kaplitt et al. claim cerebellum in claim 11, no supporting evidence is provided in the application. Thus, there is no evidence in Kaplitt et al. of tropism of any AAV for any cells of the cerebellum. There is only an unsupported claim to such tropism. One skilled in the art (i.e., a scientist in this field) would not accept such an unsupported claim as providing a reasonable expectation even for AAV2, much less AAV5.

There was no reasonable expectation of success using AAV5 as a vector, prior to the present application. At the time of the filing of Kaplitt et al. (June 6, 1995), AAV2 was the only AAV serotype which had been shown to function as a vector for gene transfer. It was not until 1997 when Chiorini et al. published the cloning of AAV4 that even a single other serotype (AAV4) could be expected to be useful as a vector for gene transfer.

That fact that AAV5 was known (but not expected to be useful as a vector) and the fact that the Kaplitt et al. claims are broad enough to read on AAV5 are not sufficient to show enablement of the use of AAV5. It is the standard of the skilled scientist, not the examination decision by the Office which determines whether there is a reasonable expectation of success. The evidence provided by applicants contradicts any assertions of the Office that the present

claims were suggested by the combination of Georg-Fries and Kaplitt et al. Thus, the rejection is faulty, and its withdrawal is believed merited.

The present rejection is legally improper. It relies on the purported scope of an allowed claim of Kaplitt et al. to define the content of that patent for prior art purposes. The courts have made it clear that the Office may not rely on the scope of the claims to assess what is taught or suggested in a prior art. According to the Federal Circuit in In re Benno, it is what is actually disclosed in the specification, not what might be covered by its claims, that must be considered in determining the impact of a patent as prior art. *In re Benno*, 768 F.2d 1340 (Fed. Cir. 1985), attached as Exhibit D. The Court acknowledged that if there is a specific disclosure in the claim of something not disclosed in the descriptive part of the specification, the claim can be used to as support to amend the specification to include the subject matter specifically disclosed in the claim. Id at 1346. There is no specific disclosure in the claims of Kaplitt et al. of any aspect of the invention not found in the description. The Office's current use of the claims of Kaplitt et al. to impute contemplation of the use of AAV5 as a vector falls squarely within the use expressly rejected by the Court. Because this is the only reference cited by the Office as allegedly providing this teaching, the obviousness rejection fails, and the claims should be allowed.

Additionally, the Office's own rules teach that the presumption of validity of the Kaplitt et al. claims is not a sufficient basis to find within it an enabling disclosure. MPEP 2121 states that the level of disclosure required within a reference to make it an "enabling disclosure" is the same no matter what type of prior art is at issue. In the present case the prior art at issue is an issued US patent that makes no mention of AAV5 or any use for AAV5. Thus, there is no suggestion, much less the required enabling disclosure for the presently claimed use of AAV5 in

Kaplitt et al. The stated justification for citing Kaplitt et al. in this rejection is that the patent contains a presumed-valid claim that covers the scope of the present claim, which by inference must be enabled. Not only is this presumption factually incorrect, it is evidence that the Office is treating this issued US patent differently than it would have treated other types of art, e.g., a journal article with the same level of disclosure. It is difficult to imagine that the Office would have based an obviousness rejection on a journal article with such a dearth of disclosure regarding any use of AAV5. Unless the Office can find some disclosure in Kaplitt et al. that supports its use by the Office in this rejection, the rejection is improper, and should be withdrawn.

Applicants acknowledge that the Office finds claims 1, 16, and 17 to be allowable.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No fee is believed due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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Gwendolyn D. Spratt — Date: 10-2-03